

Gene Section

Mini Review

AKT3 (v-akt murine thymoma viral oncogene homolog 3, Protein Kinase B gamma)

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Published in Atlas Database: July 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/AKT3ID615ch1q44.html>

DOI: 10.4267/2042/38468

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Identity

Hugo: AKT3

Other names: DKFZP434N0250; PKBG; PRKBG; RAC-PK-gamma

Location: 1q44

Note: Location in the mouse: chromosome 1 in band H4-H6.

DNA/RNA

Description

The AKT3 gene is composed of 14 exons spanning a genomic region of 354,937 bp.

Transcription

AKT3 coding sequence consists of 1,440 bp from the start codon to the stop codon.

Protein

Description

The AKT3 serine/threonine kinase consists of 479 amino acids with a calculated molecular weight of 55.8 kDa (approximate molecular weight of 59-60 kDa seen on a Western blot). The protein contains three important regions: the PH domain at the N terminus (residues 1-107), a kinase domain (residues 148-405), and a C-terminal regulatory domain (residues 406-479). A 465-amino acid splice variant lacking the serine 472 residue has been identified, which results from alternative splicing of an exon at the C terminus.

Expression

Northern blot analysis of AKT3 indicated that it is expressed in virtually all tissues, predominantly in the brain and fetal heart and at lower levels in liver and skeletal muscle. RT-PCR analysis also indicated

expression of AKT3 in a wide variety of tissues.

Localisation

Predominantly cytoplasmic; also found at the plasma membrane and in the nucleus following its activation.

Function

AKT family members are serine/threonine kinases activated following stimulation by growth factors, hormones and the extracellular matrix. AKT kinases play a key role in proliferation, cell survival, and tumorigenesis. Binding of ligands (e.g., EGF) to tyrosine kinase receptors or G-protein coupled receptors leads to the recruitment and activation of the Class 1A and Class 1B PI3K (Phosphatidylinositol 3-Kinase), respectively. The pleckstrin homology domain of AKT kinases has affinity for the 3'-phosphorylated phosphoinositides 3,4,5-trisphosphate (PI-3,4,5-P3) and PI-3,4-P2 produced by PI3K, and they are activated specifically by the latter lipid. Phospholipid binding triggers the translocation of AKT kinases to the plasma membrane. There, AKT is activated through phosphorylation of a threonine (T308 in AKT1, T309 in AKT2 and T305 in AKT3) by PDK1 and on a serine (S473 on AKT1, S474 on AKT2, and S472 on AKT3) by PDK2. Activated AKT then phosphorylates a number of different substrates involved in survival, cell cycle progression, and other pathways implicated in tumorigenesis.

Homology

AKT3 is a serine/threonine kinase and is a member of the AKT family that also includes AKT1 and AKT2. At the protein level, AKT3 shows overall 83.6% identity with AKT1 and 78% identity with AKT2. The three AKT kinases are identical in the ATP binding region, except for one residue: Ala 230 of AKT1 is conserved in AKT2 (Ala 232), but switches to Val 228 in AKT3.

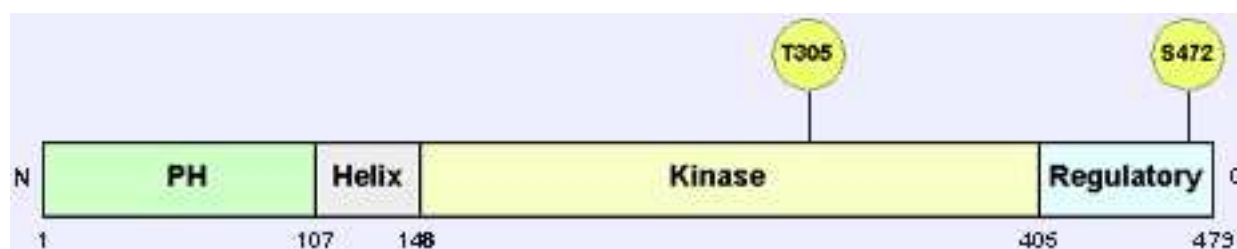


Diagram of the AKT3 protein in scale. The numbers represent specific residues. The domains are PH (Pleckstrin Homology), a short helical region, Kinase (Catalytic Kinase), and Regulatory (Regulatory Region). Indicated are the two phosphorylation sites shown to be essential for activation of AKT3: Threonine 305 and serine 472. C: Carboxyl-terminal; N: Amino-terminal.

Mutations

Note: No germline or somatic mutations were discovered through sequencing.

Implicated in

Breast cancer

Oncogenesis

AKT3 was found to be expressed at a higher level in estrogen receptor-negative breast cancer compared to estrogen receptor-positive cancers, thus possibly contributing to the more aggressive phenotype of the former. AKT3 activity was also 30- to 60-fold higher in two estrogen receptor-negative cell lines as compared to two estrogen receptor-positive cell lines.

Hepatocellular carcinoma (Hepatitis C virus related)

Oncogenesis

Using array-CGH analysis, gene copy number increases of AKT3 were found in 6 out of 19 (32%) tumors, including small, well-differentiated carcinomas. Thus, increased copies of the gene may play a potentially important role in the onset of Hepatitis C-related hepatocellular carcinoma.

Melanoma

Oncogenesis

AKT3 was demonstrated to be the predominant AKT isoform involved in melanoma tumorigenesis. Knockdown of AKT3 with siRNA was shown to decrease total phospho-AKT levels in four melanoma cell lines and in normal melanocytes. In contrast, targeting the other two AKT proteins had no effect. AKT3 protein was overexpressed in 60% of primary melanoma tumors compared to normal melanocytes. Immunoprecipitation of AKT3 followed by immunoblotting with a phospho-specific AKT antibody indicated that 43% of primary melanomas have increased AKT3 activity compared to normal controls. Moreover, siRNA-mediated knockdown of AKT3 in a melanoma cell line led to a dramatic decrease in xenograft tumor size as a result of increased apoptosis.

Ovarian cancer

Oncogenesis

AKT3 was discovered to be highly expressed in 19 out of 92 (20%) primary ovarian tumors and also expressed in a number of ovarian tumor cell lines, including two cell lines having duplications of the AKT3 gene. The high expression of AKT3 in cell lines appeared to correlate with high total phospho-AKT levels, increased proliferation, and the ability to grow in serum starved conditions. SiRNA-mediated silencing of AKT3 expression in the OVCA429 and DOV13 cell lines resulted in reduced proliferation due to inhibition of the cell cycle.

Prostate cancer

Oncogenesis

AKT3 was found to be expressed at a higher level and with a 20- to 40-fold higher activity in androgen-insensitive prostate cancer compared to androgen-sensitive prostate cancer. The loss of PTEN expression appeared to contribute to increased AKT3 activity in one of the cell lines examined. Thus, AKT3 may play a role in the more aggressive phenotype of androgen-insensitive prostate cancers.

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This article should be referenced as such:

Cheung M, Testa JR. AKT3 (v-akt murine thymoma viral oncogene homolog 3, Protein Kinase B gamma). *Atlas Genet Cytogenet Oncol Haematol*.2008;12(1):24-26.
